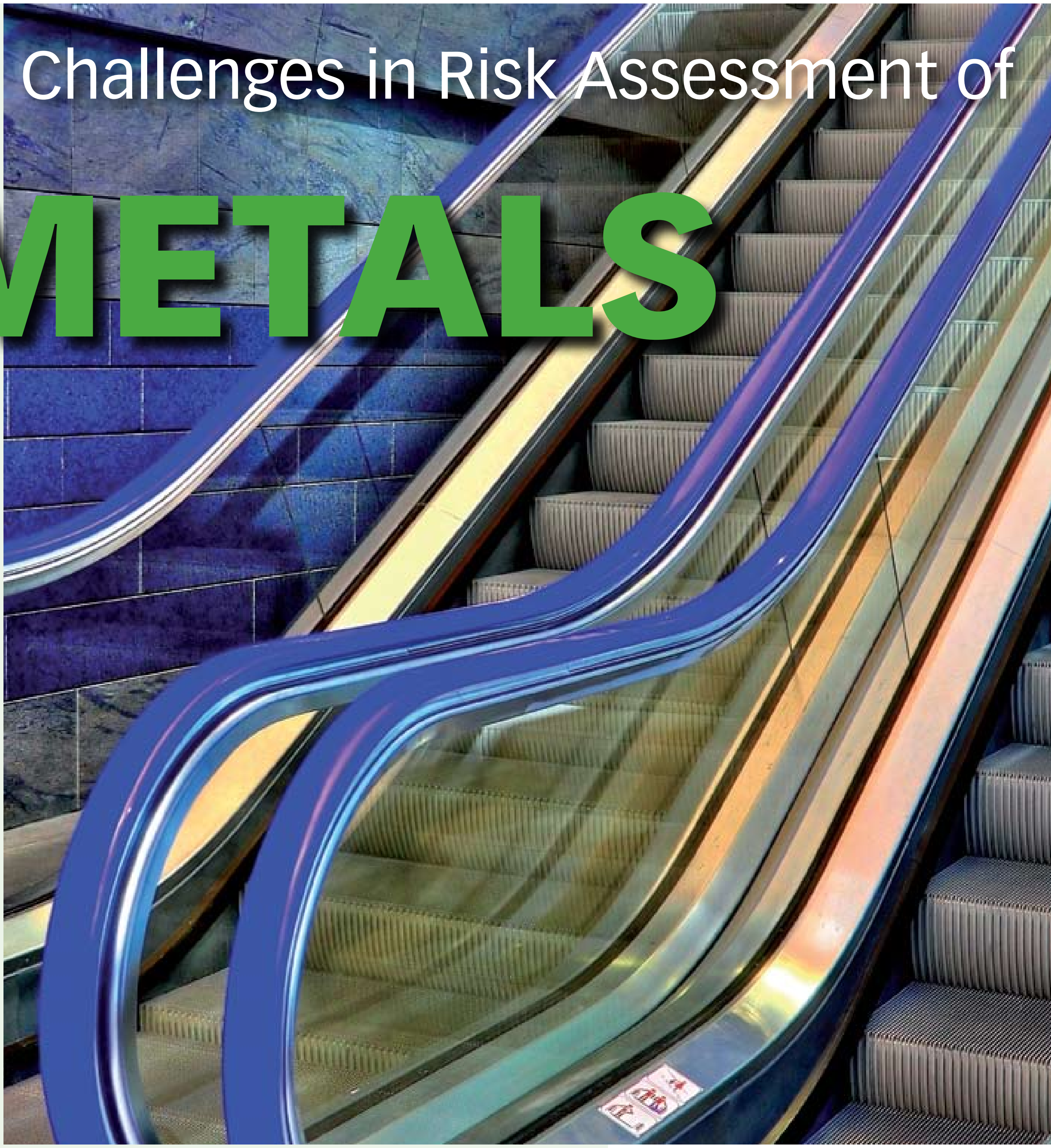
Challenges in Risk Assessment of METALS



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■ Inorganic compounds such as metals and semi-metals, and their alloys and compounds, comprise 90% of the total volume of chemicals on the market. It is, however, challenging to evaluate the health risks of metals since Reach primarily provides tools for risk assessment of organic compounds.

EU legislation on chemicals has evolved primarily to deal with organic compounds. Models to assess the risks of organic substances do not necessarily apply well to metals. Experimental data on the health effects of many inorganic compounds are lacking or inadequate to meet the requirements of Reach. On the other hand, the amount of data on certain elements is abundant but inconsistent.

Metal alloys consist of at least two elements, of which at least one is a metal. The

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Understanding Characteristics of Metals

There are several metals and semi-metals with two or more different oxidation states that are commonly used in the chemical industry. For example, there are over twenty trivalent chromium compounds in industrial use.

For chromium, the oxidation states 0, +3 and +6 are the most important. The surface of metallic chromium is instantly oxidised to chromium oxide, and thus metallic chromium does not exist on chromium surfaces or in particles.

Nickel, in contrast, does not have a similar tendency to be oxidised. In nickel-chromium alloys, chromium oxide forms a surface layer which prevents nickel from reaching the surface.

Information on surface chemistry of the alloy and release rates of individual components are important when evaluating the health effects. For example, in the case of stainless steels, the alloy surface is normally covered by a very thin layer consisting of oxides of both iron and chromium. The release rates of iron and nickel from austenitic stainless steels are approximately 0.3% and 1%, respectively, of the rates from the metals because of the passivating effect of the surface oxide layer whereas the rate of release of chromium is the same as for the metal.

In addition to total metal determination, exposure evaluation sometimes requires the use of speciation methods, i.e. determination of the solubility and ion charges of the exposing agent. For example, in the case of exposure to nickel-containing compounds, the levels of exposure to metallic nickel, nickel oxides and sulphides, and water-soluble nickel compounds should preferably be quantified separately.

Importance of particle size

With inhalation exposure, the dose absorbed by the body depends on the chemical composition and physical characteristics of the exposing compounds. It is important to know the particle size distribution and whether fibrous particles are present in the inhaled air. Particles below five micrometres in diameter reach the alveoli where their clearance is slow. Larger 5–10 micrometre particles remain in the upper respiratory tract and even larger particles in the nose.

Particles are quickly removed from the upper respiratory tract by mucus. In that case, exposure occurs via the gastrointestinal tract, and health effects have to be evaluated accordingly.

In exposure assessment, the use of biomonitoring, i.e. determination of the substance or its metabolite in, for example, blood or urine, may sometimes be helpful. In this way, information in particular about the amount of accumulated metals in the body can be obtained more reliably than by occupational hygiene measurements.

procedures to regulate alloys under Reach are still unsolved: would they be registered as multicomponent mixtures or each component separately? Furthermore, Reach implementation guidelines concerning mixtures have not been finalised.

The most widely-known alloy is steel, which is a mixture of iron and coal with other modifying elements. Nowadays, there are over 2,000 steel formulations, tailored to many purposes.

The health risk assessment of alloys is complex because even small changes in the composition have a marked affect on the physical and chemical characteristics of the material. The type and severity of health hazards may vary considerably for alloys with small differences in composition.

During exposure, the human body comes into contact with particle surfaces having a composition which can differ greatly from the composition of the actual alloy. Furthermore, the formulation of the alloy strongly affects the solubility of its components in physiological fluids.

Expanding knowledge

Many metallic compounds have been used for centuries and their harmful effects have been studied for years. However, previous testing methods are not necessarily up to present standards, and thus existing data, even if abundant, is often not adequate.

The Finnish Institute of Occupational Health (FIOH) offers expert services on chemical safety assessment under Reach. See www.ttl.fi/reach.

For example, there are many studies of soluble nickel compounds demonstrating their mutagenicity and carcinogenicity. However, risk assessment of nickel conducted by the EU indicates that there is still a need for further studies, e.g. on metallic nickel.

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1st International Course on the Health Risk Assessment of Metals, Their Alloys and Compounds under Reach
Helsinki Sept 29–Oct 1, 2008
www.ttl.fi/internet/english/training

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Metallic nickel is only slightly soluble, and thus its behaviour in the body differs from that of soluble nickel compounds. This makes it impossible to draw conclusions on the health effects of metallic nickel based on the effects of soluble nickel salts.

Scientists are interested in metallic nickel especially because of exposure to nickel-containing particles in the work environment and ambient air. Metallic nickel is a category 3 carcinogen in the EU. Labelling must include the risk phrase "R40", indicating that the substance is a suspected carcinogen. As soon as the results of new carcinogenicity studies are available, this classification will be reconsidered.

Many mutagenicity tests have also been carried out on trivalent chromium compounds. However, the results are inconsistent, even when the same compounds and the same test protocols are applied, and therefore no firm conclusions can be drawn from these studies.

These types of challenges in the risk assessment of metals necessitate a search for new approaches. Reach fortunately provides opportunities for this, and the assessment models and guidelines are constantly improving.

The writers work in the Risk Assessment and Biomonitoring Team of the Finnish Institute of Occupational Health (FIOH). Their profiles cover toxicology and industrial hygiene, and they have been involved in chemical – including metal – risk assessment projects run by the FIOH. Currently, they work under Reach in risk assessment projects for metal compounds.

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Tricky Chromium Compounds

A good example of the problems involved in risk assessment of metals is the trivalent chromium compounds. Of these, chromium oxide, chromium hydroxide hydrate and basic chromium sulphate are most commonly used. The use of chloride, nitrate and acetate salts of chromium is less common.

Most of the toxicity data on chromium compounds originate from tests with the three latter compounds. However, Reach requires the most detailed information for the substances that are produced and used in the largest amounts. This information could be obtained by testing every compound individually. This would not, however, follow the spirit of Reach, which seeks to avoid unnecessary animal testing.

One choice is to use approaches which are based on grouping substances according to similarities in their toxic effects, and to evaluate the effects of one substance based on information from another substance (read-across).

Also, computer-based QSAR (Quantitative Structure-Activity Relationships) analysis, which studies the comparability of molecular structure and biological activity for a substance, may be applied. This kind of toxicity modelling is, however, not yet very reliable.

Solubility is critical

Trivalent chromium compounds differ markedly from each other with regard to aqueous solubility, and this affects their toxicity.

Low solubility dust accumulates in the lungs, but causes fewer effects on other organs. Water soluble metal compounds, in contrast, enter better the circulatory system and can cause harmful effects in other parts of the body.

Rats exposed to aerosols of low solubility chromium(III) oxide show a mild inflammation of the alveoli. Since this substance is removed slowly, inflammation remains for a substantial period of time after exposure ends.

In a similar test with basic chromium sulphate, rats showed chronic inflammation in all parts of the respiratory tract but no accumulation of chromium in the alveoli. The inflammatory changes disappeared during the 13-week follow-up period.

Exposure to chromium sulphate weakened the general condition of rats by decreasing weight gain and changing the blood count. Chromium oxide did not cause such effects.

Thus, the effects of chromium oxide and chromium sulphate differ. That is why the toxicity data for chromium sulphate cannot be used in the setting of safe dose levels for chromium oxide.

In contrast, the aqueous solubility of metallic chromium resembles that of chromium oxide, and the surface of chromium metal oxidises rapidly to chromium oxide. Therefore, data on metallic chromium can be used for the risk assessment of chromium oxide.

The alkalinity of an aqueous solution of chromium sulphate is comparable to that of chromium chloride. Chromium chloride has been shown to cause inflammatory changes in inhalation exposure that are similar to those caused by chromium sulphate. Characteristics of these water soluble chromium compounds are similar, and thus the grouping and read-across principles can be utilised.

Multifaceted Metals

Metals and semi-metals and their compounds exist naturally in the environment, food and water. For this reason they are also the oldest toxic chemicals known.

Many metals, e.g. zinc, iron, copper, manganese and cobalt, are essential for normal functioning of the body.

Toxic metal and semi-metal compounds, such as arsenic, antimony, lead and mercury, have been used in the past to treat various illnesses. They have also been used for murder.

Nowadays, harmful dosage levels can usually be distinguished from healthy levels of essential metals. However, in some cases, for example with selenium and chromium, these levels have not yet been determined with certainty.

Problems arise when a harmful metal substitutes for an essential metal in the body, for example lead may substitute itself for calcium. The harmful substitute may then use e.g. the transportation and storage mechanisms of the essential element. Toxic metals also may substitute for metals needed at the active sites of enzymes, preventing these biological catalysts from performing their normal functions. ❒